BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

13. (Amended) The method of claim [12] 10 wherein the recombinant adenovirus vector is 231-10.

23. (Twice amended) A composition comprising [a recombinant polynucleotide encoding a Receptor Internalization and Degradation (RID) complex and] a pharmaceutically acceptable excipient [, where the RID complex includes a RIDα polypeptide and a RIDβ polypeptide] and a recombinant adenovirus that comprises a polynucleotide encoding a [RIDα] RIDα-S polypeptide, a RIDα-L polypeptide and a RIDβ polypeptide, as disclosed in SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:4, wherein the polynucleotide is operably linked to a cytomegalovirus ("CMV") promoter.

24. (Thrice amended) A recombinant adenovirus vector comprising a polynucleotide encoding a [Receptor Internalization and Degradation (RID) complex having a RIDα] RIDα-S polypeptide, a RIDα-L polypeptide and a RIDβ polypeptide, as disclosed in SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:4, wherein (a) the [which RID complex] polynucleotide is operably linked to a cytomegalovirus ("CMV") promoter, (b), [wherein] the adenovirus is replication defective and (c) [wherein] the polynucleotide is expressed upon infection of a eukaryotic cell with the adenovirus.

Remarks

Rejections under 35 U.S.C. Section 112, first paragraph.

Claims 1, 3, 4, 6, 7, 10, 12-14, 17, 19, 20 and 23-25 are rejected as not being enabling. The Examiner contends that the claims do not provide enablement for any and all cells or any and all polynucleotides that encode any and all RID polypeptides.

First, the Examiner contends that the specification does not enable the transfection of cells with a cDNA encoding RID, the expression of RID operably linked to putatively inoperable promoters, or the inhibition of apoptosis *in vivo* using an adenovirus vector. Claims 3, 6, 12, 17, 19 and 20 have been cancelled. Claims 1, 4, 7, 10, 13, 14, 23 and 24 have been amended to be drawn specifically to an *adenovirus* vector comprising a cytomegalovirus (CMV) promoter operably linked to a polynucleotide that encodes each of the component polypeptides of the RID complex, i.e. RIDα-S, RIDα-L and RIDβ, wherein the RIDα-S, RIDα-L and RIDβ polypeptide sequences are depicted in SEQ ID NOs:1, 2 and 4. As asserted by the Examiner in paper no. 13, at page 2, discussion point no. 7, lines 2-5, cotransfection of vectors comprising SEQ ID NOs:1, 2 and 4 results in the formation of a RID complex in a cell. The instant specification provides many examples of adenovirus vectors containing RIDα and β-

encoding polynucleotides enabling the protection of infected cells from apoptosis or CTL-mediated lysis. See Examples 1, 3, 4, 7 and 9, which demonstrate either protection against cell lysis or removal of Fas R or TNF R from the cell surfaces of cells transfected with polynucleotides that encode RIDα and RIDβ.

Furthermore, in the claims as amended, the polynucleotide encoding the RID components is operably linked to the CMV promoter, which is generally known in the art as a constitutively active promoter that enables the expression of any gene that is fused to it in any mammalian cell-type. Thus, the skilled artisan would reasonably expect a RID polynucleotide, which is under the control of a CMV promoter, will be expressed in any and all mammalian cell-type.

Next, the Examiner contends that even if the invention were limited to an adenovirus vector comprising polynucleotides encoding RIDα and RIDβ, the disclosure does not enable the extrapolation from in vitro cell conditions to in vivo cell conditions. The Examiner appears to be particularly concerned with the targeting of the adenovirus or RID complex to specific cells. The Examiner is reminded that Example 9 shows the effectiveness of an adenovirus, which contains a polynucleotide that encodes the RID complex components, RIDα and RIDβ, toward preventing the rejection of infected heterologous cells that had been transplanted into an immunocompetent host organism. The experiment depicted in Example 9 unequivocally demonstrates the effectiveness of the claimed invention in vivo. Claims 1 and 10 have been amended to be drawn to the *ex vivo* infection of cells, wherein the cells may then be transplanted into a patient. By limiting the claims to *ex vivo* treatment, the claims are fully supported by the experiments demonstrated in Example 9 and the putative problems associated with targeting are obviated. Furthermore, given that the adenovirus harbors at least one nonfunctional E1 gene (see specification page 32, lines 32-33), rendering said vector replication defective, the adenovirus vector can be administered to either the entire tissue to be transplanted, thus infecting every cell, or to specific regions of the tissue to be transplanted, with minimal concern that the adenovirus will spread to other tissues within the host. Furthermore, given the fact that the RID polynucleotide is operably linked to the human CMV promoter (see page 32, lines 21-23 for support for the CMV promoter), the RID polynucleotide will be actively transcribed in any and all human cells *that are infected ex vivo*.

The Examiner contends that the treatment of leukocytes with a RID complex may lead to unforeseen immunological problems in the host patient. The Examiner further contends that apoptosis treatments are "limited by their lack of specificity" (paper no. 13 page 7) and therefore may lead to injury. Claims drawn to treatment of leukocytes with RID have been cancelled without prejudice and with the right to pursue those claims in another application. Claims 1, 10 have been amended to be drawn to the treatment of cells ex vivo with RID, thus limiting the blockade of Fas R mediated cell lysis only to those cells expressing RID. The effector cells and other tissues of the host will not be affected by the treatment.

In other words, the endogenous apoptosis machinery of the host is not affected by the administration of the RID complex, and therefore normal homeostasis with regard to all other systems in the body, aside from the implanted heterologous cells, remains intact.

The Examiner continues to contend that the immunocompetent murine model is not appropriate to demonstrate graft retention. The Examiner further charges that controls demonstrating the rejection of mock infected cells were not shown. Applicants respectfully point out that on page 31, lines 14-28 of the instant specification, control experiments are described. The control mice show from none to very small tumors, whereas the experimental mice showed "much larger elipsoid [sic] masses (tumors) on both hind flanks" (p. 31, lines 24-26). Applicants assert that the Examiner has misapplied the objection to uncontrolled animal experiments.

Regarding the appropriateness of the immunocompetent mouse model of tissue rejection, the experiments presented in Examples 6, 7 and 9 demonstrate unequivocally that RID protects cells *in vitro* and likewise *in vivo* from destruction by CTL and NK cells by facilitating the removal of Fas, which has been shown in the art to be essential to graft rejection (specification page 2, lines 27-33). Therefore, the skilled artisan would have reasonable expectation of success in preventing Fas-mediated CTL/NK targeted destruction of heterologous cells transplanted into an immunocompetent host. The specification fully supports claims drawn to methods of preventing allograft rejection. Please note that claim 10 has been amended to be drawn to methods of decreasing the rejection of cells via Fas-mediation.

The Examiner contends that claims 1, 3, 4, 6, 7, 10, 12-14, 17, 19, 20 and 23-24 would have been inoperative given that the claims were drawn to only one RIDα and one RIDβ polypeptide. Claims 3, 6, 12, 17, 19 and 20 have been cancelled and claims 1, 4, 7, 10, 13, 14, 23 and 24 have been amended to be drawn to polynucleotides that encode RIDα-L, RIDα-S and RIDβ polypeptides of SEQ ID NOS:1, 2 and 4, thus obviating any rejections based upon inoperativity or lack of description.

In view of the amendments and arguments presented herein, Applicants believe that the claims are in compliance with 35 U.S.C Section 112, paragraph 1. Applicants respectfully request that the rejections be withdrawn and the claims allowed.

Rejections under 35 U.S.C. Section 112, second paragraph.

Claims 1, 10 and 17 are rejected for being vague and indefinite. Claim 17 has been cancelled and claims 1 and 10 have been amended to include the steps of "contacting" a cell with the adenovirus followed by the adenovirus "entering" the cell. These amendments are supported by language in the specification that describes cells being "infected" with various strains of adenoviruses (see at least p. 17, line 23, p. 20, line 4 and p. 21, line 22). Although the term "infect" is not identical to the terms

"contact" and "enter", the skilled virologist understands that the term "infect" connotes first a contact of a cell with a virus particle followed by the entry of that virus particle into the cell.

Claims 3, 12 and 19 are rejected for being vague and indefinite. These claims have been cancelled, thereby rendering the rejection moot.

Claims 1, 10, 17, 23 and 24 are rejected for being vague and indefinite in the use of a single polynucleotide that encodes "a complex of polypeptide." Claim 17 has been cancelled and claims 1, 10, 23 and 24 have been amended. The claims now contain language describing a polynucleotide that encodes three polypeptides that comprise the RID complex. Those constituent polypeptides are RIDα-S, RIDα-L and RIDβ. The skilled artisan understands that several polypeptides can be encoded by a single polynucleotide. Support for the description of the RID complex consisting of the RIDα-S, RIDα-L and RIDβ polypeptides can be found at least at page 11, line 31 through page 12, line 7 of the instant specification.

Claim 24 is rejected as being indefinite in the recitation of a RID complex being operably linked to a promoter. Claim 24 has been amended to refer to a polynucleotide, which encodes the constituents of the RID complex, operably linked to a CMV promoter. Thus, claim 24 is definite.

Claim 7 is rejected as being vague and indefinite in the use of the phrase "the cell in a transplant." Claim 7 has been amended to refer to the cell as a cell which is to be transplanted into a subject, thus making it clear that the cell is treated ex vivo, hence prior to transplantation in a patient.

In view of the amendments and arguments presented herein, Applicants believe that the claims are in compliance with 35 U.S.C Section 112, paragraph 2. Applicants respectfully request that the rejections be withdrawn and the claims allowed.

Rejections under 35 U.S.C. Section 102(b).

Claims 1, 3, 23 and 24 are rejected as being anticipated by Stewart et al., which teaches that the 10.4K-14.5K complex (RID complex) blocks TNF mediated cytolysis. Claim 3 has been cancelled and claims 1, 23 and 24 have been amended. As amended, claim 1 is drawn to an adenovirus comprising a polynucleotide encoding RID complex components, wherein the polynucleotide is under the control of a CMV promoter, the adenovirus lacks at least one functional E1 gene, and the apoptotic event is not mediated by TNF. Claims 23 and 24 have been amended to contain the element that the polynucleotide that encodes the RID complex polypeptides is operably linked to the CMV promoter. These claim elements distinguish the claimed inventions from the Stewart disclosure by providing the CMV promoter element, replication defectiveness via E1 deletions and/or mediation of apoptosis through pathways other than TNF, namely Fas.

In view of the amendments and arguments presented herein, Applicants believe that the claims are in compliance with 35 U.S.C Section 102(b). Applicants respectfully request that the rejections be withdrawn and the claims allowed.

Conclusion

Applicants believe that each and every issue that was raised in the office action of paper no. 13 has been sufficiently addressed and that the remaining claims are in a condition for allowance. Applicants respectfully request that the rejections against the claims be withdrawn and the claims allowed. If any other outstanding issues remain, the Examiner is invited to contact the undersigned agent.

Respectfully submitted,

Joseph E. Zahner
Reg. No. 48,224
Howell & Haferkamp, L.C.
7733 Forsyth Boulevard, Suite 1400
St. Louis, Missouri 63105
(314) 727-5188